

**Amendments to the Claims:**

This listing of claims will replace all prior versions and listings of claims in the application:

**Listing of Claims:**

1.-8. (canceled)

9. (currently amended) A method for inhibiting ~~[[a]]~~ an mRNA, comprising:

a) providing an ~~interfering hairpin~~ RNA ~~having~~ comprising the structure  $X_1$ -L- $X_2$ , wherein  $X_1$  and  $X_2$  are nucleotide sequences having sufficient complementarity to one another to form a double-stranded stem hybrid and L is a flexible loop region comprising a non-nucleotide linker molecule of 10-24 atoms in length, wherein at least a portion of one of the nucleotide sequences located within the double-stranded stem is complementary to a sequence of ~~said~~ the target mRNA; and

b) contacting ~~shRNA~~ the RNA comprising the structure  $X_1$ -L- $X_2$  with a sample containing or suspected of containing the target mRNA under conditions that favor ~~intermolecular hybridization between~~ transfection of the ~~shRNA~~ RNA comprising the structure  $X_1$ -L- $X_2$  into a cell comprising the target mRNA and the target mRNA whereby presence of the ~~shRNA~~ RNA comprising the structure  $X_1$ -L- $X_2$  decreases expression of the target mRNA~~[[.]]~~;

wherein  $X_1$  and  $X_2$  each independently comprise between about 19 to 27 nucleotides, and L comprises a polyether, a polyamine, a polyester, a polyphosphodiester, an alkylene, or a combination thereof.

10. (currently amended) A method for assaying whether a gene product is a suitable target for drug discovery comprising:

a) introducing an ~~[[sh]]~~RNA which targets ~~the~~ an mRNA of ~~the~~ a gene for degradation into a cell or organism, wherein said ~~[[sh]]~~RNA ~~having~~ comprises the structure  $X_1$ -L- $X_2$ , wherein  $X_1$  and  $X_2$  are nucleotide sequences having sufficient complementarity to

one another to form a double-stranded stem hybrid and L is a flexible loop region comprising a non-nucleotide linker molecule of 10-24 atoms in length, wherein at least a portion of one of the nucleotide sequences located within the double-stranded stem hybrid is complementary to a sequence of said ~~double-stranded RNA~~ mRNA, wherein  $X_1$  and  $X_2$  each independently comprise between about 19 to 27 nucleotides, and L comprises a polyether, a polyamine, a polyester, a polyphosphodiester, an alkylene, or a combination thereof;

b) maintaining the cell or organism of [( )]a) under conditions in which degradation of the mRNA occurs, resulting in decreased expression of the gene; and

c) determining the effect of the decreased expression of the gene on the cell or organism, wherein if decreased expression has an effect, then the gene product is a target for drug discovery.

**Please add the following new claims:**

11. (New) The method according to claim 9, wherein L is a polyether and the polyether comprises a polyethylene glycol, a polyalcohol, a propylene glycol, or a combination thereof.

12. (New) The method according to claim 9, wherein the RNA comprising the structure  $X_1$ -L- $X_2$  comprises an overhang.

13. (New) The method according to claim 12, wherein the overhang comprises 1 to 5 nucleotides.

14. (New) The method according to claim 13, wherein the overhang is a 3' overhang.

15. (New) The method according to claim 13, wherein the overhang is a 5' overhang:

16. (New) The method according to claim 9, wherein the RNA comprising the structure  $X_1$ -L- $X_2$  comprises a left hairpin.

17. (New) The method according to claim 9, wherein the RNA comprising the structure  $X_1$ -L- $X_2$  comprises a right hairpin.

18. (New) The method according to claim 9, wherein the RNA comprising the structure  $X_1$ -L- $X_2$  comprises a bulge.

19. (New) The method according to claim 18, wherein the bulge is a stem loop bulge.

20. (New) The method according to claim 18, wherein the bulge comprises a single uridine residue opposing double uridine residues.

21. (New) The method according to claim 9, wherein  $X_1$  or  $X_2$  is 100% complementary to the target mRNA.

22. (New) The method according to claim 9, wherein L is covalently attached to  $X_1$  and to  $X_2$  via an ether, an ester, a carbamate, a phosphate ester, or an amine linkage.

23. (New) A method for inhibiting a target mRNA, comprising:

a) providing an RNA comprising the structure  $X_1$ -L- $X_2$ , wherein  $X_1$  and  $X_2$  are nucleotide sequences having sufficient complementarity to one another to form a double-stranded stem hybrid and L is a loop region comprising a non-nucleotide linker molecule, wherein at least a portion of one of the nucleotide sequences located within the double-stranded stem is complementary to a sequence of the target mRNA; and

b) contacting the RNA comprising the structure  $X_1$ -L- $X_2$  with a sample containing or suspected of containing the target mRNA under conditions that favor transfection of the RNA comprising the structure  $X_1$ -L- $X_2$  into a cell comprising the target mRNA whereby presence of the RNA comprising the structure  $X_1$ -L- $X_2$  decreases expression of the target mRNA;

Applicant: SCARINGE, Stephen  
Serial No.: 10/635,108  
Filing Date: August 5, 2003  
Amendment and Reply to Nonfinal Office Action  
September 27, 2004  
Page 7 of 17

wherein  $X_1$  and  $X_2$  each independently comprise between about 19 to 27 nucleotides; L comprises a polyether, a polyamine, a polyester, a polyphosphodiester, an alkylene, or a combination thereof; L is 10-24 atoms in length; the RNA comprising the structure  $X_1$ -L- $X_2$  comprises a left hairpin RNA; and the left hairpin RNA comprising the structure  $X_1$ -L- $X_2$  comprises an overhang of 1 to 5 nucleotides and at least one bulge.